UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 1,4-Bis(bromoacetoxy)-2-butene (BBAB): Risk Assessment and Science Support Branch's Executive Summary For The Reregistration Eligibility Decision (RED)

FROM: Norm Cook, Chief
Risk Assessment and Science Support Branch
Antimicrobials Division (7510C)

TO: Julie Fairfax, Reregistration Team
Regulatory Management Branch II (RMB-II)
Antimicrobials Division (7510C)

Pesticide Chemical No.: 035605

Chemical Name: 1,4-Bis(bromoacetoxy)-2-butene (BBAB)

Case: 3030

Introduction

This document represents the Risk Assessment and Science Support Branch's (RASSB's) **final draft** of the Executive Summary for 1,4-Bis(bromoacetoxy)-2-butene (BBAB) in support of the Antimicrobials Division's (AD's) Reregistration Eligibility Decision (RED). This Executive Summary presents RASSB's findings concerning human health risks and environmental issues (an environmental risk characterization was not required for the presently-registered use patterns). This final draft can be released to those registrants who are affected by these findings.

Executive Summary

RASSB has conducted a health risk assessment and a review of environmental issues for BBAB in support of AD's RED for this chemical. This human health risk assessment and environmental review incorporate the most recent deliberations on the hazard components of risk, use and usage information, and risk assessment techniques and policies. This Executive Summary addresses the following registered BBAB slimicide uses:

1. Oil field injection water and other field water systems to control slime forming bacteria;

2. Water-based coatings as a preservative to inhibit bacterial and fungal growth; and

3. Pulp and paper mills as a slimicide in paper machines or in the preservation of paper coating formulations/chemicals.

I. Human Risks

A. Hazard/Dose Response Characterization

BBAB is moderately acutely toxic by oral and dermal routes (toxicity categories II and III, respectively). For characterizing acute toxicity by the inhalation route of exposure as well as characterizing the primary eye irritation, primary skin irritation and dermal sensitization potential of BBAB, a classification of toxicity category I is assigned and studies are waived on the basis of the known corrosivity of BBAB.

In repeated dose toxicity studies with BBAB in rats, toxicity was characterized by hyperkeratosis and hyperplasia of the non-glandular mucosa of the stomach in both male and females and edema of the stomach in females. These effects were observed at a dose of 4.5 mg/kg/day (lowest dose tested). In developmental toxicity testing with BBAB, the maternal toxicity LOAEL is 20 mg/kg/day based on an increased incidence of salivation, and the maternal toxicity NOAEL is 5 mg/kg/day. However, the developmental toxicity LOAEL is 35 mg/kg/day based on decreased mean fetal body weights, and the developmental toxicity NOAEL is 20 mg/kg/day.

There were no data submitted for evaluating dermal penetration, subchronic dermal toxicity, inhalation toxicity, reproductive toxicity, or carcinogenicity of BBAB. There were three studies submitted to study the mutagenic potential of BBAB. The results of these three studies indicate: 1) BBAB was negative in the Ames test up to cytotoxic doses; 2) BBAB was positive in mouse lymphoma cell cultures under S9 activation, but "equivocal" in the absence of exogenous metabolic activation; and 3) negative for micronucleus induction in mice.

There were no submitted neurotoxicity studies. However, signs of neurotoxicity were noted in three studies: 1) MRID 44757001: dose-related increase in salivation prior to and post-dosing and decreased activity and wobbly gait (with incidence rates and occurrence of decreased activity and wobbly gait greater in males than females); 2) MRID 44739401: hypoactivity, head held low, drooping/closed eyelid, body dragging, rocking, lurching or swaying while walking, flattened body/extended limbs, prostration, abnormal respiration, circling, splayed hindlimbs, walking on tiptoes, sporadic nasal clicks, and hunched or unkempt appearance; and 3) in an

acute dermal toxicity in rabbit with BBAB (MRID 43152401), necropsy examination revealed congested meningeal vessels in dead animals.

Endpoints - Dietary

Background: To complete a risk assessment for an indirect food use chemical for which the FDA has established a food additive regulation that specifically states that the use is "safe", the Antimicrobials Division, OPP, established a two-tiered system for toxicology testing requirements. Tier I toxicology data requirements would apply to all indirect food additives that result in residue concentrations ranging from 0-200 ppb. The requirements would consist of an acute toxicity testing battery, subchronic toxicity studies in both the rodent and non-rodent (with the inclusion of neurotoxicity testing endpoints in the rodent assay), a developmental toxicity study in the rat, a two-generation reproduction toxicity study in the rat, and a mutagenicity testing battery. The registrant may choose to combine the developmental and reproductive toxicity testing per FDA protocols, but if so, must first submit the protocol to the Agency for approval. Tier II studies would be triggered by the presence of significant (i.e. $ 200 ppb) residues in food or evidence of significant toxicity from the Tier I data set, which may include developmental/reproductive, or other systemic toxicity such as presence of neoplastic growth or significant target organ toxicity. In such cases, chronic toxicity and carcinogenicity testing would be required.

Toxicity Endpoints: Due to the lack of an adequate hazard database, RASSB has not identified toxicity endpoints for the dietary risk assessment required for the use of BBAB in pulp and paper mills in the manufacture of food-contact paper.

Endpoints - Non-Dietary (Occupational/Non-occupational)

Toxicity Endpoints: Based upon the toxicity profile and exposure patterns, RASSB concludes that the toxicology database is incomplete for determining short-, intermediate-, and long-term dermal and inhalation endpoints. However, using the available toxicity database, RASSB selected the following interim endpoint for use in the occupational/non-occupational (residential) risk characterizations: (1) *short-/intermediate-/long-term (dermal)*: LOAEL = 4.5 mg/kg/day; MOE = 300 (subchronic rat gavage study; MRID 44757001); presumed 100 % dermal absorption rate. (NOTE: An acceptable inhalation toxicity endpoint was not identified for use in an inhalation risk characterization.)

B. Dietary Exposure

Background: BBAB has a food use from its use in the manufacture of paper and paperboard that contact food. FDA has approved this use and the Regulation is codified 21 CFR 176.300 Slimacides. The Regulation states that the quantity added is not to exceed the amount necessary to accomplish the intended effect. The registered Slimacide V-10 label permits the application rate of 0.15-0.30 lb. of product (0.24 lb. active) per ton of paper produced. If all of the BBAB were to be concentrated in the paper, the paper would contain 120 ppm of BBAB.

BBAB also has a use for the preservation of water based coatings on the Busan 1210/Slimacide V-10 labels. The use of BBAB in paint is a treated article use as defined under 40 CFR

152.25(a) and is exempt from registration under FIFRA. The EPA considers that there is no dietary exposure from this use.

Dietary Exposure - Food: The *worst-case calculation* for migration of BBAB residues from treated paper to food assumes that 100% of the BBAB paper additive migrates to food. The FDA guidelines entitled, "RECOMMENDATIONS FOR CHEMISTRY DATA FOR INDIRECT FOOD ADDITIVE PETITIONS" were used as guidance for this calculation. EPA has decided to use the FDA Guidelines for this calculation because the migration data submitted by the registrant are over 30 years old and do not follow present FDA guidance, thus making the data unreliable. Based upon this approach maximum estimated residues of BBAB in food (from migration of BBAB from treated paper) are 600 ppb.

Dietary Exposure - Water: Based upon the presently registered use patterns and environmental fate characteristics of BBAB (rapid hydrolysis and biodegradation), RASSB concludes that BBAB is not likely to occur in drinking water sources.

C. Dietary Risk Characterization

Because pertinent toxicity data are lacking, RASSB is deferring the dietary risk assessment required for the use of BBAB in pulp and paper mills in the manufacture of food-contact paper. The additional hazard data required will depend upon the calculated, or measured, residues of BBAB expected in food. (See Section G. below for discussion of additional data required.)

D. Occupational/Non-Occupational Exposure/Risk Characterizations

Handler Exposures/Risks: Since chemical-specific exposure data are lacking for BBAB RASSB utilized the Pesticide Handlers Exposure Database (PHED) to perform the applicator (handler) exposure and risk characterizations. Based upon the registered use patterns RASSB identified two levels of potential occupational handler exposures: (1) *primary handlers*: for manufacturing settings, persons who are handling BBAB pesticide products for use as a slimicide in paper machines, in the preservation of papermaking coating formulations/chemicals, in oil field injection systems, in pulp and paper mills, and as a preservative in slurries, emulsions, and water-based coatings, such as paints; and (2) *secondary handlers*: for non-occupational (e.g., residential) or commercial settings, persons who are handling paint products to which BBAB has been added.

For *primary handlers (occupational only)*, RASSB concludes that short-,intermediate-, and long-term, non-cancer, dermal risks are *unacceptable* (MOE $<$ 300) for two scenarios: (1) mixing/loading liquids for paint manufacturing (open-pour liquids when 1000 gallons are treated per day) (MOE = 64); and (2) mixing/loading liquids for general preservative use (open-pour liquids) (MOE = 38).

For *secondary handlers (occupational and non-occupational [residential])*, RASSB concludes that short-, intermediate-, and long-term, non-cancer, dermal risks are *unacceptable* (MOE $<$ 300 [dermal]) for all painting scenarios -- application via: (1) paint brush (MOEs = 1.2 - 2.4); (2) airless sprayer (MOEs = 0.5 - 0.9); and (3) aerosol can (MOEs = 17 - 21). (NOTE: Adequate exposure data are not available to assess application via roller.)

Postapplication Exposures/Risks: Chemical-specific data are not available for RASSB to determine occupational or non-occupational (residential) exposures and risks. However, RASSB concludes that, compared to handler exposures, post-application exposures and risks are likely to be minimal.

E. Aggregate Exposure/Risk Characterizations and FQPA Considerations

Because pertinent toxicity data are lacking RASSB has not performed aggregate exposure and risk characterizations nor addressed other FQPA considerations.

F. Uncertainties

There are a variety of uncertainties associated with both the dietary and non-dietary exposure and risk characterizations. These uncertainties affect the integrity of both assessments and usually can be minimized with submission of pertinent hazard and/or exposure data. A full listing of uncertainties is provided in the human exposure, toxicology, and risk characterization science chapters.

G. Data Needs

In order to reduce the uncertainties associated with the dietary and non-dietary exposure and risk assessments, and to allow RASSB to finalize exposure and risk characterizations, the following data are required in support of reregistration of BBAB:

For Dietary Risks:

Using FDA guidelines RASSB has calculated maximum estimated residues of BBAB in food (from migration of BBAB from treated paper) of 600 ppb. Based upon this level (600 ppb) the following toxicity data are required to support reregistration:

1. A 90-day non-rodent study with the inclusion of neurotoxicity testing endpoints(OPP Guideline 82-1, OPPTS Number 870-3100);
2. A two-generation reproductive toxicity study in the rat (OPP Guideline 83-4, OPPTS Number 870-3800);
3. A developmental toxicity study in the rabbit (OPP Guideline 83-3, OPPTS Number 870-3700);
4. A chronic study in non-rodents (OPP Guideline 83-1, OPPTS Number 870-4100);
5. A combined chronic toxicity/carcinogenicity study in the rat (OPP Guideline 83-5, OPPTS Number 870-4300); and
6. A carcinogenicity study in the mouse (OPP Guideline 83-2, OPPTS Number 870-4200).

However, the registrant may decide to rebut this maximum level of BBAB in food (600 ppb) by submitting an acceptable food migration study using presently approved FDA migration study techniques. If under such circumstances these new data indicate BBAB residues in food are less than 200 ppb, then the following toxicity data are required:

1. A 90-day non-rodent study with the inclusion of neurotoxicity testing endpoints(OPP

Guideline 82-1, OPPTS Number 870-3100); and
2. A two-generation reproductive toxicity study in the rat (OPP Guideline 83-4, OPPTS Number 870-3800).

For Non-Dietary (Occupational/Non-occupational) Risks:

1. A dermal penetration study (OPP Guideline 85-7, OPPTS Number 870-7600) and/or a 90-day dermal study (OPP Guideline 82-3, OPPTS Number 870-3250);
2. A 28-day inhalation study at one dose level (with 2.5% BBAB) (OPP Guideline 82-4, OPPTS Number 870-3465); and
3. An oral neurotoxicity screening battery study (OPP Guideline 81-8, OPPTS Number 870-6200).

II. Environmental Risks

A. Ecological Hazards

BBAB has an LD_{50} of 196 mg/kg to mallard ducks on an acute oral basis and is categorized as moderately toxic. The mallard duck dietary LC_{50} is > 5000 ppm and is categorized as practically nontoxic to avian species on a subacute dietary basis. BBAB has acute freshwater fish LC_{50}s which are in the range of 0.025 to 0.057 ppm, and BBAB is categorized as very highly toxic to freshwater fish on an acute basis. BBAB is also categorized as highly toxic to freshwater invertebrates on an acute basis with an EC_{50} of 0.14 ppm. These were the only ecological hazards data available for BBAB.

B. Environmental Exposures/Risks

The presently-registered use patterns are not expected to have significant effluents to the environment, or will have discharges which are regulated by the National Pollution Discharge Elimination System (NPDES). Considering this, RASSB did not perform environmental exposure and risk characterizations.

C. Endangered Species

Because the presently-registered use patterns are not expected to have significant effluents to the environment, or will have discharges which are regulated by the National Pollution Discharge Elimination System (NPDES), RASSB has not conducted exposure/risk characterizations for endangered species. However, the Agency's Endangered Species Protection Program is expected to become final at some point, and at that time RASSB will determine if chemicals such as BBAB fall under the criteria of this program.

D. Data Needs

Presently-registered labels prohibit use of BBAB in offshore oil recovery systems. If the registrant decides to remove this prohibition, the following acute toxicity testing with estuarine/marine fish and invertebrates is required for BBAB Technical Grade Active Ingredient (TGAI). These data will be used for labeling purposes and consist of the following studies

(Guidelines: 850.1025, 850.1035, 850.1045, 850.1055, and 850.1075):

Acute LC_{50} with an estuarine/marine fish species;
Acute LC_{50}/EC_{50} with an estuarine/marine mollusk species; and
Acute LC_{50} with an estuarine/marine shrimp species.

E. Environmental Labeling

The following label statements are recommended for all presently-registered products:

> This product is toxic to fish and aquatic invertebrates. Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans, or public water unless this product is specifically identified and addressed in an NPDES permit. Do not discharge effluent containing this product to sewer systems without previously notifying the sewage treatment plant authority. For guidance contact your State Water Board of Regional Office of the EPA.

Presently-registered labels prohibit use of BBAB in offshore oil recovery systems. However, submission of the estuarine/marine fish and invertebrate studies would provide RASSB with the data needed to adequately label the oil recovery use and provide for removal of the above restriction.

In closing, the above represents RASSB's executive summary for the human and environmental exposures and risks of presently-registered BBAB use patterns. If there are questions on the above, please feel free to contact me or Allen Vaughan.

Attachments

Science Chapters:

Appendix 1: Product Chemistry (barcode: D251928; electronic documents: D251928.mem; D251928.wpd)
Appendix 2: Dietary Exposure (barcode: D251933; electronic documents: D251933.mem; D251933.wpd)
Appendix 3: Human Exposure (barcode: D251930; electronic document: D251930.wpd)
Appendix 4: Toxicology (barcode: D251929; electronic documents: D251929.wpd; tabl4-1.123)
Appendix 5: Epidemiology/Incidents (barcode: D265945; electronic document: D265495.wpd)
Appendix 6: Human Risk Characterization (barcode: D251936; electronic document: D251936.wpd)
Appendix 7: Environmental Fate (barcode: D251932; electronic documents: D251932.mem; D251932.wpd)
Appendix 8: Ecological Effects (barcodes: D251931, D251935; electronic documents: D251931.mem; D251931.wpd)

NOTE: Environmental Modeling: No science chapter required.

cc: Jonathan Chen
Winston Dang
Wanda Jakob
Tim Mcmahon
Kathryn Montague
Siroos Mostaghimi
Allen Vaughan